

What is claimed is:

1. An interfering hairpin RNA having the structure X₁-L-X₂, wherein X₁ and X₂ are nucleotide sequences having sufficient complementarity to one another to form a double-stranded stem hybrid and L is a loop region comprising a non-nucleotide linker molecule,

5 wherein at least a portion of one of the nucleotide sequences located within the double-stranded stem is complementary to a sequence of said target RNA.

2. The hairpin RNA of claim 1, wherein each of said X₁ and X₂ nucleotide sequences
10 comprise between about 19 to 27 nucleotides.

3. The hairpin RNA of claim 1, wherein said non-nucleotide linker L is selected from the group consisting of polyethers, polyamines, polyesters, polyphosphodiesters, alkynes, attachments, bioconjugates, chromophores, reporter groups, dye labeled RNAs, and non-naturally occurring nucleotide analogues or combinations thereof.

4. The hairpin RNA of claim 3, wherein said polyether is selected from the group consisting of polyethylene glycol, polyalcohols, polypropylene glycol or mixtures of ethylene and propylene glycols.

20 5. The short interfering RNA of claim 1, wherein the double-stranded segment of the hairpin structure is formed between two perfectly matched nucleotide sequences.

6. The short interfering RNA of claim 1, wherein the double-stranded segment of the
25 hairpin structure is formed between two imperfectly matched nucleotide sequences.

7. The short interfering RNA of claim 1, further comprising a 3' overhang sequence.

8. The short interfering RNA of claim 1, further comprising an internal overhang.

30 9. A method for inhibiting a mRNA, comprising:
a) providing an interfering hairpin RNA having the structure X₁-L-X₂, wherein

X₁ and X₂ are nucleotide sequences having sufficient complementarity to one another to form a double-stranded stem hybrid and L is a loop region comprising a non-

nucleotide linker molecule, wherein at least a portion of one of the nucleotide sequences located within the double-stranded stem is complementary to a sequence of said target RNA; and

5 b) contacting shRNA with a sample containing or suspected of containing the mRNA under conditions that favor intermolecular hybridization between the shRNA and the target mRNA whereby presence of the shRNA the target mRNA.

10. A method for assaying whether a gene product is a suitable target for drug discovery comprising:

10 a) introducing an shRNA which targets the mRNA of the gene for degradation into a cell or organism, wherein said shRNA having the structure X₁-L-X₂, wherein X₁ and X₂ are nucleotide sequences having sufficient complementarity to one another to form a double-stranded stem hybrid and L is a loop region comprising a non-nucleotide linker molecule, wherein at least a portion of one of the nucleotide sequences located within the double-stranded stem is complementary to a sequence of said double-stranded RNA;

15 b) maintaining the cell or organism of (a) under conditions in which degradation of the mRNA occurs, resulting in decreased expression of the gene; and

20 c) determining the effect of the decreased expression of the gene on the cell or organism, wherein if decreased expression has an effect, then the gene product is a target for drug discovery.